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---------- Message Contents

In preparation for our call this morning, I am sending the latest version of a list of Grand Challenges in the telegraphic form that Rick and I developed in Dublin. (Rick: This includes slightly edited versions of those you sent me plus a preliminary version of the agricultural proposal.)

1) Curing HIV and Other Latent Viral Infections

Roadblock
We do not have the ability to pharmacologically target either the biochemical mechanisms active in latently infected cells and/or a way to uniformly activate latent viral infections.

Challenge
To identify unique molecular targets in latently infected cells and/or to pharmacologically trigger the uniform activation of viruses in latently infected cells to then target the destruction of all cells harboring HIV (or other pathogenic viruses, such as HBV or herpes viruses).

Potential Benefits
Creates the possibility of a short course cure for HIV- a less expensive and logistically more reasonable alternative to the current life-long approach to attempt to control a chronic infection.

2) Male Contraception

Roadblock
We do not know the molecular machinery that controls spermatogenesis and sperm function (e.g. in fertilization) as the basis for rational contraceptive development.

Challenge
To systematically identify unique molecular targets amenable to drug development for novel contraceptives.

Potential Benefits
Provides a new approach to preventing unwanted pregnancy.

3) Water Purification for Health

Roadblock
We currently need point-of-use purification technology that addresses the absence of an ideal filtration or alternative purification strategy.

Challenge
To create long-lived, effective, affordable technologies for point-of-use water purification that eliminates parasites, pathogenic bacteria and viruses as well as toxins from drinking water to prevent water borne infectious diseases such as those that cause infantile diarrhea, parasitic infections or toxin-induced poisoning.

Potential Benefits
Marked reduction in childhood intestinal infections, etc.

4) Biomarkers for the Accurate Detection of Disease

Roadblock
We currently lack the technologies to discover and measure markers for many critical health conditions, for example to distinguish asymptomatic infection by a pathogen from clinical disease.

Challenge
To develop methods for the measurement of nucleic acids, proteins, metabolites and any combination of those that define and distinguish clinical states that result from infection, malnutrition, and other health conditions common in the developing world

Potential Benefits
- Distinguishing malarial illness from benign parasitemia
- Diagnosing latent infection with Mycobacteria
- Defining micronutrient deficiencies
- Distinguishing acute respiratory and gastrointestinal disease states and defining the causes

5) Immune-Based Infectious Disease and Immune Status Diagnostics

Roadblock
We currently cannot readily measure the human immune system in order to "see" what it has "seen" and thus lack the ability to know and interpret human exposures, immune status and current infections.

Challenge
To develop novel measurement tools to determine the repertoire of human immune responses via the ability to query, quantify the responses, and fully interpret the human immune system.

Priority Areas
- Diagnosis of Infectious Diseases
- Determination of Immunization Status

6 & 7
Vector Population Control

Roadblock

We have not solved the full range of problems that would allow us to either replace an insect vector population with one incapable of transmitting a disease organism or of controlling population numbers by means other than insecticides or environmental control.

Challenges

- To develop all of the components needed to alter insect vector populations (e.g. Anopheles or Aedes), including vector transgenesis, a successful gene drive mechanism for super-Mendelian inheritance in the population, and full safety via absolute species specificity

- To create an efficient way to raise and introduce modified organisms, for example, sterile males or males carrying female conditional lethal genes, using genetic approaches that create large numbers of altered vectors that will reduce the wild population via breeding.

Priority Areas

- Malaria
- Trypanosomiasis
- Dengue

8 & 9
Smart Sprays for Vector Control

Roadblock

Currently used insecticides are limited by the development of resistance and environmental concerns.

Challenges

- To identify the molecular components of chemical and biochemical pathways controlling vector behavior and their attraction to humans, as well as identification and validation of chemical or biological products that could be used in sprays to target and alter those pathways.
- To identify and validate novel targets for molecularly directed insecticides.

Priority Areas

- Mosquitoes – for malaria control

- Tse Tse Flies – for trypanosomiasis control

10) Strategies for Therapeutic Viral Vaccines

Roadblock
We do not know how to direct the immune system to specifically and efficiently kill cells chronically infected with viruses during the course of infection.

Challenge
To establish methods to mount a specific and effective immune attack on cells chronically infected with important viral pathogens without inducing autoimmunity.

Priority Areas
- TB
- HBV
- HCV

11, 12, 13, 14

Creating Ideal Children's Vaccines

Roadblock
We currently lack a multiplicity of technologies to optimize the effective and efficient delivery of basic vaccines to children in resource-poor settings.

Challenges
This roadblock can be addressed via four challenges:
- To create technologies to make all vaccines thermostable
- To establish novel delivery systems for immunogens so that long term, high quality memory and immune protection can be achieved via delivery of a single dose
- To solve the problems of expression, epitope immunodominance and other challenges of creating effective multi-antigen vaccines
- To create effective needle-free delivery systems that optimize protective immune response via mucosal, oral and/or transdermal approaches

Technological breakthroughs for one or any combination of those challenges would be sought.

15) Rational and Predictive Approaches to Vaccine Development

Roadblock
We cannot readily identify or predict what antigen(s) will be essential targets for an effective immune response and what aspect of the immune response is responsible for effective immunity to an organism.

Challenge
To develop systematic and definitive methods to establish the true correlates of effective immunity---both the nature of the immune response and the targets of that immune response---to guide the development of preventive and therapeutic vaccines.

Priority Areas
- Malaria
- TB

16) Creation of Live Attenuated Vaccines

Roadblock
Our inability to rapidly master attenuation of pathogenic organisms.

Challenge
To use genetic manipulation and high through-put assessment of host interactions to create effective and fully safe live organism vaccines that optimize immune presentation and are incapable of causing disease.

Priority Areas
All major infectious diseases that lack effective vaccines

17) Creating Effective Immunogens From Antigens

Roadblock
We are current unable to produce antigens that predictably elicit high affinity antibodies against the determined structure of a known or candidate immunogen.

Challenge
To develop methods to construct antigens that predictably elicit such antibodies by establishing the desired target structure, assuring that it is seen by the immune system and is the immunodominant epitope presented.

Priority Areas
Eliciting neutralizing antibodies for HIV

18) Creating Immunity Without Immunization

Roadblock
Currently, the only way to deliberately create immunity is by immunization, a process that is unpredictable in generating the desired immune response.

Challenge
To develop immune cell engineering that creates cells with the properties of delivering a specific effective antibody that can safely and permanently be delivered and that will work in all individuals in order to produce, when needed, effective immune protection.

Priority Areas
Neutralization of HIV

19) Cures for Persistent, Latent and "Dormant" Microbial Infections

Roadblock
Currently, we lack the ability to kill bacteria or other organisms once they have established latent or "dormant" states.

Challenge
To identify and fully credential pathogen and/or host components essential to the survival of latent or dormant microbial infections and to use this information for the development of targeted drugs

Priority Areas:

- TB
- Antibiotics that kill quiescent or relatively quiescent bacterial infections

20) Solving and Avoiding Drug Resistance

Roadblock
We do not know either how to design drugs or to choose drug targets that minimize the development of drug resistance or know how to target the microbial mechanisms of the acquisition and/or spread of drug resistance.

Challenge
To develop and demonstrate novel approaches to drug design that minimize the probability of resistance and/or determine how to inhibit drug resistance mechanisms from arising within or spreading through populations of micro-organisms.

Priority Areas:

- Malaria
- TB
- HIV
- Antibiotic-sensitive bacteria

21) Countering malnutrition with agricultural biotechnology

Roadblock

Despite important advances in plant molecular biology, we still lack the ability to deliver important nutritional factors to malnourished populations as components of widely consumed crops.

Challenge

To develop a range of new and efficient technologies to allow widely used crops (such as rice, sorghum, corn, bananas, tomatoes, etc) to provide a diversity of micronutrients, including, for example, Vitamins A (retinol) and E, iron, iodine, zinc, selenium, sulfur-containing amino acids.

Potential Benefits

- Reduced malnutrition
- Reduced susceptibility to infectious diseases and other chronic diseases